



Persistence of Serogroup C Antibody Responses following Quadrivalent Meningococcal Conjugate Vaccination in United States Military Personnel

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Naval Health Research Center

Report No. 13-07

Naval Health Research Center
140 Sylvester Road
San Diego, California 92106-3521

Vaccine 32 (2014) 3805–3809

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Persistence of serogroup C antibody responses following quadrivalent meningococcal conjugate vaccination in United States military personnel

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ARTICLE INFO

Article history:
Received 5 September 2013
Received in revised form 27 April 2014
Accepted 1 May 2014
Available online 14 May 2014

Keywords:
Meningococcal vaccine
Conjugate
Polysaccharide
Antibody persistence

ABSTRACT

Serogroup C meningococcal (MenC) disease accounts for one-third of all meningococcal cases and causes meningococcal outbreaks in the U.S. Quadrivalent meningococcal vaccine conjugated to diphtheria toxoid ($MenACYW_D$) was recommended in 2005 for adolescents and high risk groups such as military recruits. We evaluated anti-MenC antibody persistence in U.S. military personnel vaccinated with either $MenACYW_D$ or meningococcal polysaccharide vaccine (MPSV4). Twelve hundred subjects vaccinated with $MenACYW_D$ from 2006 to 2008 or MPSV4 from 2002 to 2004 were randomly selected from the Defense Medical Surveillance System. Baseline serologic responses to MenC were assessed in all subjects; 100 subjects per vaccine group were tested during one of the following six post-vaccination time-points: 5–7, 11–13, 17–19, 23–25, 29–31, or 35–37 months. Anti-MenC geometric mean titers (GMT) were measured by rabbit complement serum bactericidal assay (rSBA) and geometric mean concentrations (GMC) by enzyme-linked immunosorbent assay (ELISA). Continuous variables were compared using the Wilcoxon rank sum test and the proportion of subjects with an rSBA titer ≥8 by chi-square. Pre-vaccination rSBA GMT was <8 for the $MenACYW_D$ group. rSBA GMT increased to 703 at 5–7 months post-vaccination and decreased by 94% to 43 at 3 years post-vaccination. GMT was significantly lower in the $MenACYW_D$ group at 5–7 months post-vaccination compared to the MPSV4 group. The percentage of $MenACYW_D$ recipients achieving an rSBA titer of ≥8 decreased from 87% at 5–7 months to 54% at 3 years. There were no significant differences between vaccine groups in the proportion of subjects with a titer of ≥8 at any time-point. GMC for the $MenACYW_D$ group was 0.14 μg/mL at baseline, 1.07 μg/mL at 5–7 months, and 0.66 μg/mL at 3 years, and significantly lower than the MPSV4 group at all time-points. Anti-MenC responses wane following vaccination with $MenACYW_D$; a booster dose is needed to maintain protective levels of circulating antibody.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; DMSS, Defense Medical Surveillance System; DoD, Department of Defense; DoDSR, Department of Defense Serum Repository; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; GMT, geometric mean titer; LLQ, lower limit of quantitation; MenACYW, quadrivalent meningococcal conjugate vaccine; $MenACYW_D$, quadrivalent meningococcal conjugate vaccine conjugated to diphtheria toxoid; MenC, Serogroup C *Neisseria meningitidis*; MPSV4, quadrivalent meningococcal polysaccharide vaccine; NHRC, Naval Health Research Center; rSBA, rabbit complement serum bactericidal assay; VE, vaccine effectiveness.

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http://dx.doi.org/10.1016/j.vaccine.2014.05.001

1. Introduction

In the United States, serogroups B, C and Y *Neisseria meningitidis* each account for approximately one-third of meningococcal cases [1]. From 1998 to 2007, serogroup C (MenC) disease resulted in the highest case fatality ratio (14.6) among the three serogroups [1]. MenC often results in more severe sequelae in its survivors and has a predilection to cause outbreaks [2–4]. Sequence type (ST) 11/electrophoretic type (ET) 37 clonal complex was responsible for outbreaks in U.S. army military recruits in the 1960s and continues to cause outbreaks in the U.S. today [1,5]. Although disease rates for all serogroups are at a historic low, morbidity and mortality among cases remains unchanged.

Prior to 2005, quadrivalent (A, C, Y, W) meningococcal polysaccharide vaccine, MPSV4 (*Menomune*®, Sanofi Pasteur, Swiftwater, PA, USA), was used routinely in U.S. military recruits to reduce the risk of disease during basic training. However, routine vaccination of the general population was not recommended because of its limited duration of protection. In 2005, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination of adolescents and other persons at high risk for meningococcal disease with a newly licensed quadrivalent meningococcal conjugate vaccine (MenACYW) [6]. Two quadrivalent meniningococcal conjugate vaccines are currently available for adolescents in the U.S. $MenACWY_D$ (*Menactra*®, diphtheria toxoid conjugate, Sanofi Pasteur, Swiftwater, PA, USA) was licensed in 2005 and $MenACWY_{CRM}$ (*Menveo*™, CRM-197 conjugate, Novartis Vaccines, Cambridge, MA, USA) in 2010. The ACIP recommended use of either vaccine for adolescents aged 11–18 years and other persons at increased risk for meningococcal disease, including military recruits and first year college students living in residential housing. Upon licensure, quadrivalent meningococcal conjugate vaccines were expected to provide protection for at least 5–10 years. However, a limited number of persistence studies conducted during clinical trials suggest antibody waning occurs faster than previously predicted [7,8].

To address increasing concern for limited duration of protection following vaccination with meningococcal conjugate vaccine, in January 2011 the ACIP recommended a booster dose for adolescents on or after their 16th birthday to provide optimal protection throughout the period of increased risk (16–21 years of age). Booster doses continue to be recommended every 5 years for high risk groups, such as those with certain immunologic disorders, as well as military personnel who continue to be at increased risk [9]. However, data supporting the optimal interval for vaccination of these high risk groups are limited. The objective of this study is to evaluate antibody persistence to MenC following vaccination with $MenACWY_D$ in military personnel to inform US public health policy for quadrivalent meningococcal vaccines. Serologic responses over a 3 year period are compared to military recruits who were routinely vaccinated with meningococcal polysaccharide vaccines (MPSV4) prior to licensure of conjugate vaccines.

2. Materials and methods

2.1. Study design and participants

We conducted a retrospective cohort study among U.S. military service personnel previously vaccinated with either quadrivalent meningococcal conjugate ($MenACWY_D$) or polysaccharide (MPSV4) vaccine. Eligibility criteria included receipt of one dose of MPSV4 from 2002 to 2004 or $MenACWY_D$ from 2006 to 2008, availability of sera prior to vaccination, and at least one sample within 3 years post-vaccination. Individuals with a history of ≥2 doses of meningococcal vaccine were excluded. Subjects meeting the eligibility criteria were selected from the U.S. Department of Defense's (DoD) Defense Medical Surveillance System (DMSS) electronic database. DMSS integrates medical surveillance data for over ten million individuals who have served in the U.S. military since 1990 [10,11]. Sera that had been previously collected and subsequently stored in the Department of Defense Serum Repository (DoDSR) as part of public health surveillance were used to determine serological responses to meningococcal vaccines.

To determine persistence of antibody responses to MenC following vaccination with MPSV4 or $MenACWY_D$, 1200 subjects, 600 subjects per vaccination group, were randomly selected from DMSS. Basic demographic information, including sex, age and race, and meningococcal vaccination history were obtained from DMSS. Pre-vaccination samples from all subjects were tested to determine baseline levels. Two hundred subjects, 100 subjects per vaccination group, were evaluated during one of six post-vaccination time-points: 5–7 months, 11–13 months, 17–19 months, 23–25 months, 29–31 months, or 35–37 months. Only one post-vaccination sample per subject was tested.

The study was determined exempt from human subjects research review by the Human Subjects Offices at the Naval Health Research Center (NHRC) and Centers for Disease Control and Prevention (CDC).

2.2. Serological responses

Serum bactericidal antibody titers to MenC were measured by a validated rabbit complement serum bactericidal assay (rSBA) using the target strain C11 [12,13]. Viability counts were determined with an automated colony counter (Synbiosis Protocol, United Kingdom). A titer of 1.33 was assigned to sera with no activity in the initial serum dilution of 1:4. Continuous titers were interpolated from 3-fold serum dilutions. Each sample was assigned a continuous titer resulting in ≥50% killing compared to control wells. The proportion of subjects with rSBA titers at or above the putative protective threshold of 8 was calculated [14,15]. A more conservative cutoff of 128 was also used to assess decay of immune responses over time. Serum IgG anticapsular antibody concentrations were determined using a standardized enzyme-linked immunosorbent assay (ELISA) [16]. The concentration of specific IgG antibodies in human sera was calculated relative to a human standard reference serum pool, CDC 1992 [17]. Antibody concentrations below the lower limit of quantitation (LLQ) of 0.001 μg/mL were assigned the LLQ. Data were captured with Gen5™ (BioTek) and analyzed using ELISA for Windows (CDC, Atlanta, GA). The percent of subjects with IgG antibody concentrations at or above 2 μg/mL was determined [18,19]. Testing was performed blinded to vaccine type and time-point.

2.3. Statistical analysis

Sample size calculations with a two-sided alpha of 0.05 and 80% power were based on previous adult immunogenicity studies of meningococcal conjugate and polysaccharide vaccines to determine the proportion of subjects with a threshold of ≥8 for rSBA titers and ≥2 μg/mL for IgG responses [8,20]. Statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). Geometric mean titers (GMT) for rSBA and geometric mean concentrations (GMC) for ELISA were calculated for each vaccine group per time-point. Because the log-transformed data were not normally distributed, continuous variables were compared using the Wilcoxon rank sum test at each time point. A Chi-square test was used to compare categorical variables, including the proportions of subjects with rSBA titers ≥8 and ≥128, as well as the increase in 4-fold response compared to baseline for each time-point. Comparisons with a two-sided P value ≤0.05 were considered statistically significant. P-values for multiple tests across the seven time points

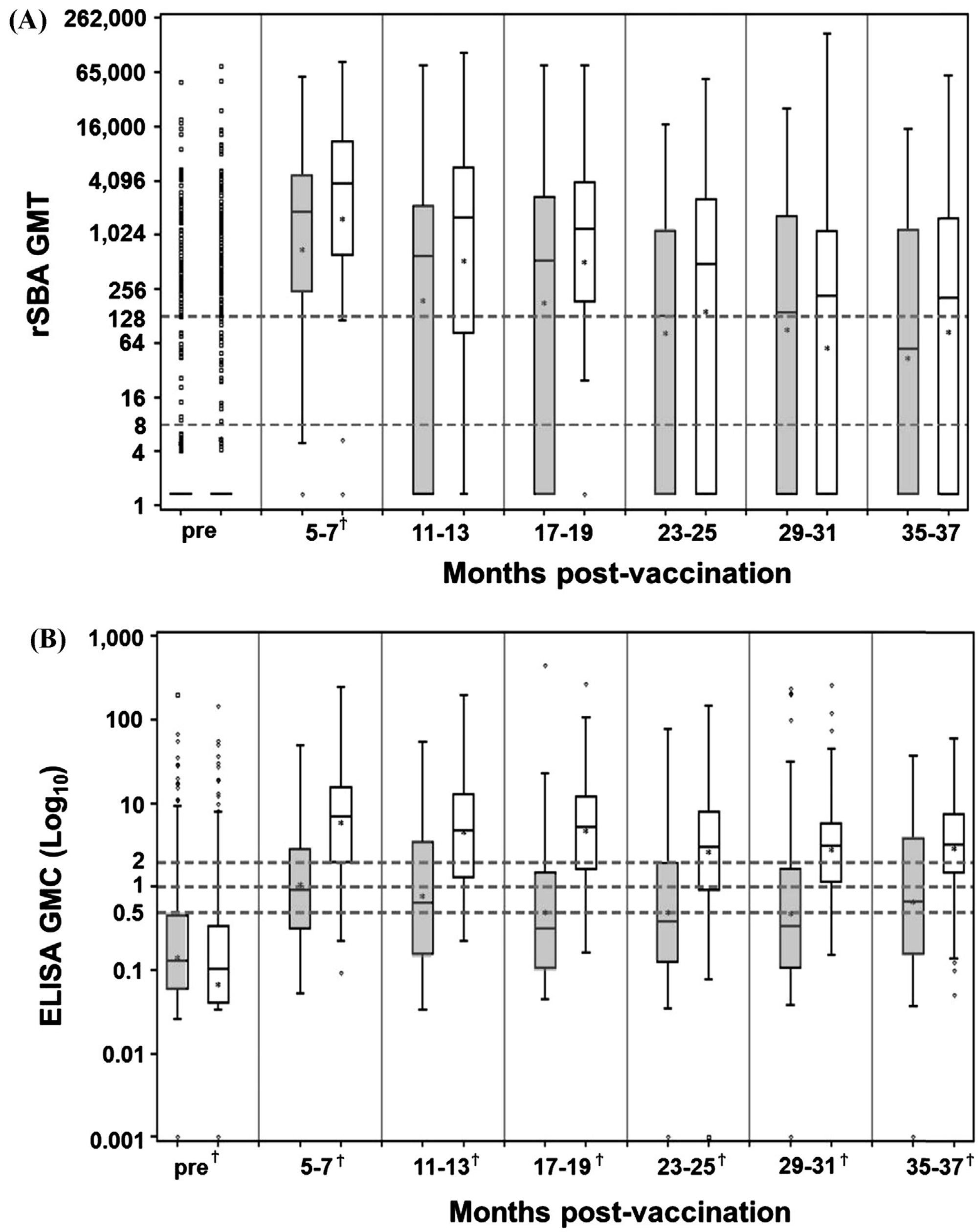

Fig. 1. Box plots of (A) serum bactericidal titers measured by rSBA and (B) antibody concentrations measured by ELISA to MenC by months post-vaccination in MenACWY_D (gray bars) or MPSV4 (white bars) vaccine recipients. The box is defined by the 25th and 75th percentiles of the distribution; the horizontal line within the box represents the median or 50th percentile and the star (asterisk (*)) signifies the mean. Vertical lines extend to the most extreme observation that is less than 1.5× the interquartile distance (75th–25th percentiles) and the diamonds (◊) and boxes (□) correspond to moderate and severe outlying assay values, respectively. Cross bars (†) denote statistical significance ($P < 0.05$) between vaccine groups for that time-point.

were adjusted for multiple comparisons by multiplying tested P-values by 7 and comparing them to 0.05 in a test for significance.

3. Results

Among the 1200 subjects evaluated, 83% were male and 68% were white. The mean age at the time of vaccination was 20.5 years (range, 17–37) for MenACWY_D and 20.0 years for MPSV4 (range, 17–34). There were no significant differences in sex and race between vaccine groups. Serum bactericidal activity and antibody concentrations to MenC were measured for all subjects prior to vaccination. Post-vaccination rSBA titers and antibody concentrations were analyzed in 1192 and 1190 subjects, respectively. Reasons for exclusion included insufficient volume for testing and failure to pass rSBA acceptance criteria for a reportable titer. The number of serum samples excluded was similar between vaccine groups.

3.1. MenC serologic responses

Baseline rSBA GMT was <8 for both vaccine groups (Fig. 1a). Five to 7 months after vaccination, rSBA GMT increased to 703 and 1557 in MenACWY_D and MPSV4 groups, respectively. GMT decreased by >93% for both groups by 3 years post-vaccination (GMT 43 and 85 for MenACWY_D and MPSV4 groups, respectively). There were no significant differences in GMT between vaccine groups except at 5–7 months post-vaccination (adjusted $P < 0.05$). GMC were <0.20 μg/mL for both vaccine groups prior to vaccination (Fig. 1b). Anti-MenC GMC increased to 1.07 μg/mL in the MenACWY_D group

Table 1
Proportion of subjects with a serum bactericidal titer ≥8 and ≥128 to meningococcal serogroup C and a 4-fold rise compared to baseline by time since vaccination with $MenACWY_D$ or MPSV4.

Months after vaccination	Number of subjects		Percent with rSBA titer ≥8		Percent with rSBA titer ≥128		Percent with ≥4-fold rise compared to baseline	
	$MenACWY_D$	MPSV4	$MenACWY_D$	MPSV4	$MenACWY_D$	MPSV4	$MenACWY_D$	MPSV4
Pre	600	600	21	23	18	19	–	–
5–7	99	99	87	87	80	85	77	79
11–13	99	99	73	80	65	74	65	72
17–19	99	100	72	83	64	78	55	71
23–25	100	99	69	68	51	61	64	51
29–31	99	98	66	59	53	52	57	53
35–37	100	100	54	62	46	55	45	55

and 6.00 μg/mL in the MPSV4 group 5–7 months after vaccination. By 3 years post-vaccination, GMC decreased by 38% (0.66 μg/mL) for $MenACWY_D$ and 51% (2.95 μg/mL) for MPSV4. GMC were significantly different between vaccine groups for all time-points, with the conjugate vaccine resulting in lower IgG antibody concentrations than the polysaccharide vaccine (adjusted $P < 0.0035$).

3.2. Proportion of subjects above a given threshold for Men C

The percentages of subjects achieving a serum bactericidal titer of ≥8 and ≥128 against MenC and a 4-fold rise compared to baseline are shown in Table 1. The proportion of subjects in both vaccine groups with titers ≥8 and ≥128 at 3 years compared to 5–7 months post-vaccination decreased by 29–38% and 35–43%, respectively. There were no significant differences between vaccine groups in the proportion of subjects with a titer of ≥8, ≥128, or 4-fold increase from baseline at any time-point. The proportion of subjects with MenC antibody concentrations ≥2.0 μg/mL was significantly lower in the $MenACWY_D$ group at all post-vaccination time-points (Table 2).

4. Discussion

This large-scale observational study of antibody persistence to MenC in U.S. military personnel demonstrates waning of immunity within 3 years following vaccination with either $MenACWY_D$ or MPSV4. No significant differences between the two vaccine groups were observed in the percentage of subjects at or above an rSBA titer of 8, the putative protective level for MenC. Lower antibody concentrations among $MenACWY_D$ recipients may be explained by the quantity of antigen in each vaccine as $MenACWY_D$ contains 1/10 the serogroup C antigen of MPSV4. Despite lower antibody concentrations, functional activity (as measured by rSBA) was comparable between vaccine groups, suggesting other immunologic responses elicited by conjugate vaccines likely contribute to overall protection. Conjugate vaccines are T-dependent and therefore induce immunologic memory and more rapid anamnestic responses after repeated doses, with antibody level typically several folds greater than after initial vaccination. This boost response has been demonstrated after a repeat dose of $MenACWY_{CRM}$ 5 years after primary vaccination [21]. Additionally, avidity maturation following initial vaccination elicits highly specific antibodies with greater bactericidal activity, and could thus explain the similarity in rSBA response despite significantly different antibody concentrations between vaccine groups.

The importance of maintaining circulating antibodies to prevent MenC disease has been reported in monovalent MenC conjugate vaccine post-licensure studies in the United Kingdom [22,23]. Previously vaccinated subjects that developed MenC disease demonstrated antibody levels and bactericidal activity comparable to unvaccinated patients, despite evidence of immunologic memory [22]. Anamnestic responses can take up to 5 days to develop and thus may not be sufficiently rapid enough to prevent disease [23].

Several U.S. studies have evaluated MenC antibody persistence greater than 1 year following vaccination with quadrivalent conjugate vaccines in adolescents [7,8,21]. These studies were conducted as extension studies within clinical trials, evaluated antibody persistence in <500 subjects per study, and provided duration of antibody response for only one time-point post-vaccination. Serologic responses varied between studies and could be attributed to differences in study population, type of protein conjugate used in the vaccines, and assay methods and reagents (e.g., complement source). Despite these differences, these studies demonstrated waning of immunity to MenC of 60–72%, 35–80%, and 56% at 2, 3 and 5 years after vaccination, respectively. Additionally, one of the studies suggested early evidence of waning at 2 years following vaccination $MenACWY_D$ and $MenACWY_{CRM}$, regardless of brand type [7]. Evaluation of immune responses during the first month following vaccination was not conducted in our study; however, we were able to demonstrate an antibody decay of over 93% in anti-MenC serum bactericidal activity and over 38% in antibody concentrations during multiple sampling periods between 6 months and 3 years following vaccination with $MenACWY_D$.

Preliminary estimates from a quadrivalent meningococcal conjugate vaccine effectiveness (VE) study conducted in over 60% of the US population demonstrates a decrease in VE from 82% (CI = 54%–93%) for adolescents vaccinated <1 year earlier to 59%

Table 2
Proportion of subjects with antibody concentration ≥2 μg/mL to meningococcal serogroup C by time since vaccination with $MenACWY_D$ or MPSV4.

Months after vaccination	Number of subjects		Percent with anti-MenC IgG ≥2 μg/mL	
	$MenACWY_D$	MPSV4	$MenACWY_D$	MPSV4
Pre	600	600	10	7
5–7[a]	98	99	39	75
11–13[a]	99	99	34	67
17–19[a]	99	100	22	70
23–25[a]	100	99	23	59
29–31[a]	99	98	22	62
35–37[a]	100	100	37	67

[a] $P < 0.05$, level of significance.

(CI = 5%–83%) for those vaccinated 3 to <6 years earlier [24]. These data correlate well with our study in which almost half of $MenACWY_D$ recipients did not demonstrate putative protective titers 3 years following a single dose.

This study supports the recent ACIP recommendation for a booster dose of meningococcal conjugate vaccine for adolescents to maintain protection through late adolescence. Decay in antibody responses following a single dose of $MenACWY_D$ should be used to inform policy recommendations regarding repeat vaccination among military personnel at increased risk. As the routine adolescent booster dose is implemented, continued vaccine effectiveness studies, disease surveillance, and antibody persistence studies will be important to evaluate the impact of the booster dose on duration of protection.

Acknowledgements

We thank Doug Avery, for assistance with quality assurance of serum bactericidal assays, and Julianne Nielsen of the Naval Health Research Center who performed confirmatory assays. We are grateful to the Armed Forces Health Surveillance Center and the Department of Defense Serum Repository for providing the specimens and respective data. The views expressed in this work are those of the authors and do not reflect the official policy of the Department of the Navy, Department of Defense, or the US Government. Approved for public releases; distribution is unlimited. This research has been conducted in compliance with all applicable federal regulations governing the protection of human subjects in research. This work was performed with institutional support provided by the Military Vaccine Agency (MILVAX), Military Infectious Diseases Research Program (MIDRP), contract #W911QY-08-D-022.

Conflict of interest. The authors report no conflicts of interest.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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REPORT DOCUMENTATION PAGE

1. REPORT DATE (DD MM YY)
28 01 13

2. REPORT TYPE
Journal submission

3. DATES COVERED (from – to)
From 2002 to 2008

4. TITLE
Persistence of Serogroup C Antibody Responses Following Quadrivalent Meningococcal Conjugate Vaccination in United States Military Personnel

5a. Contract Number: W911QY-08-D-022
5b. Grant Number:
5c. Program Element Number:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number:
Military Vaccine Agency (MILVAX), Military Infectious Diseases Research Program (MIDRP)

6. AUTHORS
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8. PERFORMING ORGANIZATION REPORT NUMBER
13-07

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10. SPONSOR/MONITOR'S ACRONYM(S)
NMRC/BUMED

11. SPONSOR/MONITOR'S REPORT NUMBER(s)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES
Vaccine 2014, 32(30), 3805-9.

14. ABSTRACT

Pre-vaccination rabbit serum bactericidal assay (rSBA) geometric mean titer (GMT) was <1:8 for the MenACWY$_D$ group. rSBA GMT increased to 703 at 5-7 months post-vaccination and decreased by 90% at 3 years post-vaccination. GMTs were significantly lower in the MenACWY$_D$ group at 11–13 and 17–19 months post-vaccination compared with the MPSV4 group. The percentage of MenACWY$_D$ recipients achieving a rSBA titer of ≥1:8 decreased from 87% at 5-7 months to 54% at 3 years. There were no significant differences in the proportion of subjects with a titer of ≥1:8 at any time point between vaccine groups. Geometric mean concentrations (GMCs) decreased from 1.1 µg/mL at 5-7 months to 0.6 µg/mL at 3 years in the MenACWY$_D$ group and were significantly lower than GMCs in the MPSV4 group at all time points.

15. SUBJECT TERMS
meningococcal vaccine, meningococcal disease, military

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	18a. NAME OF RESPONSIBLE PERSON
UNCL	UNCL	UNCL	UNCL	16	Commanding Officer

18b. TELEPHONE NUMBER (INCLUDING AREA CODE)
COMM/DSN: (619) 553-8429

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39-18